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(54) PROCESS FOR THE SEPARATION OF BINARY MIXTURES

(71) We, FARBWERKE HOECHST AKTIENGESELLSCHAFT vormals Meister Lucius & Brüning, a German Company of, 6230 Frankfurt (Main) 80, P.O. Box 800320, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a process for the separation of the components of binary mixtures.

A hitherto proposed method for resolving racemic mixtures into their optical isomers consists in inoculating a supersaturated solution of the racemate with crystals of one antipode, allowing the latter to crystallize selectively and subsequently separating it from the mother liquor which is enriched with the other antipode. Thus a racemate can be resolved into its antipodes by alternate use of the (+)- and (−)-form as inoculating material.

The abovementioned process, designated as "the swing method", is difficult to carry out on a technical scale. In order to prepare the super-saturated solution, a number of process steps is required before each crystallization cycle, for example heating of the mother liquor, saturation with racemic material, filtration for removing undesired inoculation crystals and cooling down to the crystallization temperature. If the super-saturated state is brought about in another way, for example by concentration of saturated solutions, addition of precipitating agents or action on the dissociation equilibriums, further measures must be taken to control the composition of the solution especially when the entire operation is carried out in a continuous manner.

The present invention is based on the observation that the above mentioned disadvantages can be by-passed by omitting the use of a solvent.

The present invention accordingly provides a process for the separation of the components of a binary mixture which binary mixture has a minimum melting point in the range of from −100° to +150°C, preferably from −80° to +130°C and especially from −50° to +110°C, and whose composition is within the area embraced by the extrapolated branches of the melting point curves below their intersection point, preferably the eutectic composition, with the exception of such pairs of substances that form mixed crystals and/or congruently or incongruently melting compounds with one another, wherein the binary mixture, is cooled in form of a homogeneous melt, in the absence of additives, to a temperature in the range of from 0.05 to 15°C, preferably from 0.5 to 6°C below the eutectic temperature, inoculated with crystals of one of the components, and allowed to crystallize selectively, advantageously at a constant temperature, until the residual melt contains less of the inoculated component than would correspond to the eutectic proportion, the crystals then being separated from the residual melt.

The process of the present invention will now be described in more detail by way of example only, with reference to Figure I of the accompanying drawings, which is a melting point vs. composition diagram of a mixture of components A and B. If a melt of substances A and B having the composition corresponding to the eutectic point P, which satisfies the conditions mentioned above, is super cooled, for example to a temperature T, and if inoculation crystals of the component A are added, then substance A which is contained in the melt grows on these crystals. However the separation sets in only if the temperature is so chosen that the growth of

crystals of component B is not simultaneously initiated by excessive supercooling. Spontaneous crystallization of component B can always be prevented by using a homogeneous melt, i.e. a melt which is free from inoculation crystals, and by maintaining the above mentioned temperature limits. If desired the suitable crystallization temperature can be determined by simple preliminary tests.

While component A is crystallizing, component B is accumulating in the melt so that the composition of the latter changes, starting from p, in the direction of point b. As soon as the composition of the melt reaches this point b which lies in the extrapolated branch of melting point curve AP, the system comes to rest and component A no longer crystallizes out. Hence, at b the melt is saturated with A.

The amount of component A separated from the melt represents the maximum quantity of component A obtainable at the temperature T. It is also possible, however, to carry out the separation of crystals from the melt, for example by filtration, before the state of equilibrium is reached at b. This is the preferred method if the crystallization proceeds slowly because the crystallization speed is greatest when the composition of the melt is in the proximity of p. It is essential only that the inoculation crystals grow, or that the melt becomes enriched in the other component, so that the melt composition becomes different from that at p.

In a preferred method of carrying out the process of the invention, the separated melt which is enriched with substance B can be subsequently inoculated with crystals of component B in the same temperature range. During the growth of these inoculation crystals, the composition of the melt returns from b through p to a.

The separation of B before establishment of the eutectic mixture would in this case be possible in a hitherto known manner, for example by crystallization at the eutectic temperature T_e. The transgression of the eutectic composition of the melt in direction of point a, and thus the growth of crystalline B in a eutectic melt, is, however, only possible in the temperature range according to the invention. Therefore, in order to save energy, it is advantageous to carry out the whole process isothermically in the indicated temperature range.

The separation of crystalline B ceases as soon as the composition of the remaining melt reaches the extrapolated branch of the melting point curve of B, for example at the temperature T at point a. After isolation of the crystalline component B, for example by filtration, the melt which is now enriched with A can be used again for the separation of A by inoculation with crystalline A. It is possible to repeat this cycle until the melt is largely used up. The molten phase which has been separated by filtration needs no special working up before it is subjected to the next crystallization cycle.

The process of the invention may be carried out batchwise or continuously. In continuous operation, the melt which has been separated into the solid components must be continuously replenished with super cooled eutectic, while the crystalline components must be removed continuously from the filtration devices (for example an elutriating line, rotary filter or similar device). If necessary, the isolated components may be purified in a known manner, for example by drop melting, whereby the adhering residual melt is removed and can be advantageously recycled into the separation process.

Preferably the homogeneous melt is continuously and isothermally recycled through two crystallizers each containing crystals of one of the components, preferably while continuously refilling with liquid eutectic phase and continuously separating the formed crystals and removing inoculation crystals when transferring the melt from one crystallizer to the other.

The foregoing description shows that the process of the invention is suitable for the resolution of binary mixtures which exhibit a eutectic melting behaviour. Binary systems that form mixed crystals or systems which form congruently in incongruently melting solid phases do not fall within the scope of the present invention.

The resolution of a eutectic binary system is only possible under conditions where the supercooled melt is super-saturated with both components, i.e. in the area embraced by the branches of the melting point curves extrapolated in the direction of the lower temperatures, as shown in Figure 1.

Since the amount of eutectic to be separated by each cycle rises with decreasing temperature, one will endeavour to use as low a process temperature as possible. This is opposed, however, by the fact that the stronger supercooling the undesired component shows a growing tendency spontaneously to form crystals, which necessitates a limitation on the degree of cooling to temperatures in the range of from 0.05 to 15°C, preferably from 0.5 to 6°C, below the eutectic temperature. The difficulty which increases with falling temperatures, of removing the crystallization heat isothermally, as well as the tendency towards spontaneous crystallization of the undesired component which increases with increasing melting points, limit the process of the present invention to binary mixtures having eutectic temperatures in the range of from −100 to +150°C, preferably from −280 to +120°C, and especially from −50 to +110°C.

As a purely physical separation method the process of the invention is largely indepen-

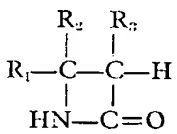
dent of the chemical nature of the substances subjected to it, as long as the process is carried out within the limits as hereinbefore defined. These, however, render the process especially suitable for binary mixtures of organic compounds.

In general, binary eutectic mixtures of organic components can also be separated by methods other than by crystallization. However if the binary mixture is a racemic mixture of two optical isomers, separation by a method other than selective crystallization is only possible at much greater expense. Therefore, the process of the invention can be used with particular advantage for the resolution of a racemic mixture into its antipodes. This case will be explained in greater detail by way of example only with reference to Figure 2 of the accompanying drawings.

As shown in Figure 2, the diagram of the melting point curves is symmetrical. If a racemic mixture of the melt P is supercooled to about the temperature T (state p) and inoculated with crystals of the laevorotatory form, these continue growth in the melt. Accordingly, the melt becomes enriched in the dextrorotatory form, and thus becomes dextrorotatory, until the system is no longer supersaturated with the (−)-form and comes to rest at b^+. If the crystalline (−)-form is separated and the remaining dextrorotatory melt is inoculated with the pure (+)-antipode, the whole process is repeated in a mirror image like manner. The melt changes its composition from b^+ through p to a^-. Numerous repetitions of this cycle lead to total resolution of the racemate into its antipodes.

A resolution into antipodes from a super cooled melt has already been suggested by R. M. Secor, Chem. Rev. 63, 300 (1963). However, the essential precondition of the process, i.e. operation between the branches of the melting point curves which are extrapolated over their intersection point, was not recognized.

Racemic mixtures, preferably racemic mixtures of organic enantiomers, which can be resolved by the process of the present invention are not limited by their chemical properties but only by their physical properties. The racemates should melt in the range of from −100 to +150°C, preferably from −80 to +120°C, especially from −50 to +110°C, without racemizing. The process of the present invention may be applied with particular advantage for the resolution of racemic β-lactams of the general formula



in which R_1 represents an alkyl group having from 1—5 carbon atoms, or a vinyl or phenyl group, R_2 and R_3 each represents hydrogen atoms, a methyl group or, together, an alkylene radical having from 3—5 carbon atoms. Since the molecule must have at least one centre of asymmetry, R_3 must not stand for a hydrogen atom if R_1 and R_2 are identical.

As example of β-lactams there may be especially mentioned (±) - 4 - methyl - azetidinone - 2, (±) - 4 - vinyl - azetidinone - 2, (±) - 4 - phenyl - azetidinone - 2, (±) - trans - 3,4 - dimethyl - adezitidinone - 2, and (+) - 4 - methyl - 4 - n - propyl - azetidinone - 2.

A preferred method of carrying out the process of the present invention will now be described by way of example only with reference to Figure 3 of the accompanying drawings which shows apparatus suitable for carrying out the process. Referring to Fig. 3 both crystallization vessels 1 and 2 are provided with a filtration device, for example a filter plate 3, and can be brought to the process temperature by means of a cooling or heating jacket 4. For this purpose, for example a heating or cooling medium may be cycled through the jacket, entering it at 5 and leaving it at 6. Both crystallizers are filled with the racemate to be resolved and, when the temperature of the process is reached, the racemate is inoculated, for example that in 1 with the laevorotatory antipode and that in 2 with the dextrorotatory antipodes; after some time, the melt in 1 which has become dextrorotatory can be transferred through filter 3 and through line 7 by means of pump 8 into vessel 2. Here, the dextrorotatory crystals act as inoculating crystals for the separation of the dextrorotatory component. The melt in 2 which has simultaneously become laevorotatory is transferred in an analogous manner through filter 3, line 9 by means of pump 8 into vessel 1. The crystals remain in the crystallizers and act continuously as inoculating material. If a portion of the crystals in vessels 1 and 2 is removed from time to time or continuously and the melt is replenished with fresh racemate through line 10, the system operates continuously. It is also possible to operate the system in such a manner as to resolve as far as possible into the solid antipodes only the quantity of racemate introduced into 1 and 2. In this case, however, the process must be discontinued if a content of solid of 25—35% in the solid melt is reached, because the elimination of the crystallization heat from the magma-like reaction mixture does not proceed sufficiently rapidly to maintain an isothermal process. Finally, it is also possible to collect each melt filtered off in a surge tank before transferring it into the other crystallizer. This measure prevents the negation of already effected resolution, when, for

example, the dextrorotatory melt from 1 is mixed with the levorotatory melt in 2.

The antipodes which can be obtained according to the invention without the use of auxiliaries, in a simple manner and with high space-time yields, have superior action in all those cases where stereochemical influences are of importance. For example, in asymmetrical drugs which are obtained in the form of racemates, one antipode is, in most cases, much more active than the other one. The antipodes of β-lactams yield, upon polymerization, stereo-regular, isotactic polymers which are far superior to the racemic polymers with regard to their physical properties.

The tests described hereinafter were carried out using the device shown in Figure 4 of the accompanying drawings. Vessels 1 and 2 are provided with filter plates 3 and jackets 4 and are kept at the respective process temperature of the cooling medium which enters at 5 and leaves at 6. Slowly rotating stirrers in both vessels ensure sufficient heat exchange. The liquid phases in 1 and 2 can be aspirated into receivers 11 and 12 for which purpose an underpressure is established at socket 13. During the crystallization in 1 and 2, a weak stream of an inert gas is introduced through 13, which, when valves 14 are closed, prevents the liquid phase from running off from 1 and 2 and which gas can escape at 15. For exchanging the melts, these are first aspirated into 11 and 12 with valves 14 closed and then, with valves 14 open, transferred using excess pressure at 13 and by means of mammoth pumps 8 into the other crystallization vessel. A heat insulator prevents the melts from taking up or giving off heat during the transfer cycle.

The following Examples illustrate the invention:

Example 1

The crystallizers 1 and 2 (Figure 4), each having a capacity of 300 ml, were each filled with 250 ml of a molten mixture of 2 parts of *o* - chloro - nitrobenzene and 1 part of *p* - chloro - nitrobenzene. The mixing proportion corresponded almost to that of the eutectic. Water which was kept at a temperature of 10 to 11°C was cycled through jackets 4 and maintained the melts at a temperature of 11—12°C. Then, 0.5 g of pure crystallized *o* - chloro - nitrobenzene was introduced into vessel 1 and 0.5 g of the pure p-isomer was introduced into vessel 2. After 15 minutes, the melt which had not crystallized was filtered off with suction.

The filter residues (3—5 g, each) consisted of crystals which were practically pure and of a film of adhering melt. Depending on the size of the crystals, the purity of the total residue was 70—90% by weight of the desired component.

The crystals however, were left on the filters and the melt was transferred from 11 into vessel 2 and the melt from 12 was transferred into vessel 1 by means of pump 8. After a crystallization period of 15 minutes, filtration with suction was carried out and the melts were exchanged. This time, about 15 g of residue remained on the filters. After a total of 5 crystallizations, the crystals were removed from the filters by melting and collected separately. 25—35 g of *p* - chloro - nitrobenzene melting at 55—65°C were obtained, corresponding to a purity of about 70% of *p*-compound. 50—60 g of *o*-compound having a melting point of 21—25°C were obtained, corresponding to a purity of 80% of *o*-chloro - nitrobenzene. The components thus enriched could be separated by conventional methods into the pure compounds and eutectic.

Example 2

A. In the device as that shown in Figure 4, the crystallizers 1 and 2 were filled each with 250 g of racemic trans - 3,4 - dimethyl - azetidinone - (2) (melting point +23.7°C). Separation was carried out at +20°C. The batch in vessel 1 was inoculated with 0.2 g. of (−) - trans - 3,4 - dimethyl - azetidinone - (2), that in vessel 2 with the same quantity of the (+)-antipode. The antipodes required for the first inoculation were prepared in the manner described under B.

Crystallization was terminated after 30 minutes by filtration with suction. The melt in vessel 11 showed a rotation α_D^{21} of +2°C, thus it contained about 4% of (+)-form, whereas the melt in vessel 12 showed a rotation α_D^{21} of −1.5°C, thus containing about 3% of the (−)-form. These melts were transferred into the crystallizers 2 and 1, respectively, and crystallization, filtration with suction and exchange of the melts were repeated 7 times. 150 g each of residual melt were obtained which showed an α_D^{21} of +2.8° and −1.8°, respectively, and which were used again after having been replenished with racemate. The crystals were molten and collected separately: of each 100 g, showing an $[\alpha]_D^{21}$ of −62.9° (c=3; water), corresponding to an optical purity of 84% and an $[\alpha]_D^{21}$ of +64.4° (c=3; water) corresponding to an optical purity of 86%, respectively, were obtained.

Thus, 84 and 86 g of antipodes were isolated from 0.5 kg of racemate within 4 hours. This corresponds to a space-time yield of approximately 80 g/liter/hour.

The enriched enantiomers were purified by recrystallization. Melting point: +60.6°C, $[\alpha]_D^{21} = \pm 50.6°$ (c optional, in the racemate), $[\alpha]_D^{21} = \pm 74.7°$ (c=3; water).

B. The quantity required for the initial inoculation was prepared as follows:

655 g of thionyl chloride (5.5 mols) were introduced dropwise, at +30°C, in the course of 3.5 hours, to 990 g of (±) - trans - 3,4 - dimethyl - azetidinone - (2) - (10.0 mols) in 2.5 l of methanol. After removal of the solvents by distillation under reduced pressure, 1740 g of crystals remained behind, which yielded, after recrystallization from a mixture of methanol and ethyl acetate, 1576 g (9.4 mols) of (±) - threo - α - methyl - β - amino - butyric acid methyl ester hydrochloride melting at 109—110°C (94% of the theory). 1400 g (8.4 mols) of this hydrochloride were dissolved in 3.5 l of methanol, combined with the solution of 193 g of sodium in 3.5 ml of methanol, combined with the solution of 193 g of sodium in 3.5 l of methanol, filtered with suction to remove the NaCl, and the filtrate was combined with the solution of 1260 g of L - (+) - tartaric acid (8.4 mols) in 3 liters of methanol. From this solution, which had been clarified while still hot, there precipitated at room temperature 813 g of enriched (+) - threo - α - methyl - β - aminobutyric acid methyl ester - (+) - hydrogen - tartrate having a melting point of 83—84°C and an $[\alpha]_D^{21}$ of +17.0° (c=3; water) and after cooling to 0°C, again 490 g, having a melting point of 68—76°C, and an $[\alpha]_D^{21}$ of 13.3° (c=3; water). The 490 g mentioned above yielded, upon recrystallization from 2.5 l of methanol, 253 g of hydrogen-tartrate having a melting point 82—84°C and an $[\alpha]_D^{21}$ of +16.7° (c=3; water). This quantity, together with the first 813 g, yielded upon recrystallization from 4 l of methanol, 660 g of (+) - threo - base - hydrogen - tartrate having an $[\alpha]_D^{21}$ of +17.7° (c=3; water). Renewed recrystallization from methanol yielded 407 g of (+) - threo - α - methyl - β - aminobutyric acid methyl ester - (+) - hydrogen - tartrate having a melting point of 82—86°C and an $[\alpha]_D^{21}$ of 18.3° (c=3; water). By further 4 recrystallization of a sample, the optically pure diaestereomer having a melting point of 86°C and an $[\alpha]_D^{21}$ of +20.7° (c=3; water) was obtained.

281 g (1 mol) of the enriched hydrogen-tartrate were dissolved in 1.5 liter of methanol, saturated with ammonia, cooled again and the ammonium tartrate was filtered off with suction. From the filtrate, the ester base was isolated by fractional distillation on a Vigreux column. Boiling point: 77—80° C/25 mm Hg, $n_D^{20}=1.4310$, $[\alpha]_D^{21}=+28.8°$ (substance; $d^{21}=0.9724$). Yield: 101 g (77% of the theory) of (+) - threo - α - methyl - β - aminobutyric acid methyl ester having an optical purity of about 70%.

For obtaining the optically active β-lactam, 98 g of this ester (0.75 mol) were introduced dropwise into 1400 ml of 0.8N - ethereal ethyl - magnesium bromide solution (1.13 mol), the whole was kept boiling for 30 minutes and then 300 ml of semi-concentrated hydrochloric acid were allowed to fun into the vigorously stirred suspension while cooling with ice. The aqueous phase was rendered weakly acid and then extracted three times with chloroform, the extracts together with the ether phase were concentrated and the oily residue was subjected to distillation. 28 g of partly crystallized β-lactam were obtained, of which 79% constituted the trans-isomer. Boiling point 60—65°C/0.4 mm Hg. From this crude product, there were obtained by crystallization 16.8 g of enriched (+) - trans - 3,4 - dimethyl - azetidinone - (2); melting point: 39°C; $[\alpha]_D=+41.2°$ (c=3; water).

150 g of racemic melt were inoculated at +17°C with 1 g of the above preparation, whereupon 123 g of residual melt showing an optical rotation α_D^{21} of −0.5° (substance) were obtained. Therefrom, there was prepared enriched (−) - trans - 3,4 - dimethyl - azetidinone - (2) by bringing the total residue melt to crystallization by cooling and allowing the batch to get to +24°C, whereby the impurities mainly became liquid and dropped from the crystals, i.e. by the so-called "drop melting process", until 20 g of crystals remained. These yielded, after melting up and renewed crystallization, 16 g of melt showing an optical rotation α_D^{21} of −8.7° (c=3; water). With these crystals, the selective crystallization described under A was initiated.

Example 3

2 Batches of each time 250 g. of racemic 4 - methyl - azetidinone - (2) (melting point −12.4°C) were inoculated at −13.9°C, in the device as shown in Figure 4 with the antipodes which had been obtained from the respective pure enantiomers of β - (α - phenyl - ethyl) - amino - butyric acid over the following intermediate stages:

a) preparation of the acid chloride with thionyl chloride at about 20 to about 25°C,

b) cyclization of the acid chloride-hydrochloride thus obtained by boiling under reflux of the benzene solution with N,N - dimethyl - aniline, and

c) splitting off of the α - methyl - benzyl group with sodium in liquid ammonia.

(melting point: +26.7°C; $[\alpha]_D^{20}=\pm 8.30°$ (c optional, in the racemate). After each crystallization period of 30 minutes, the batches were filtered with suction, the melts were exchanged and subjected again to crystallization. During that time, the melts showed values of the optical rotation which oscillated between +0.35 and −0.33°. After completion of the 6th and 13th cycle the crystals that had formed were isolated by melting and collected separately. 274 g of melt were recovered. The levorotatory product (111 g. $\alpha_D^{21}=-5.96°$ (in substance)) contained 80 g of the pure antipode, and.

had thus an optical purity of 72.5%. The dextrorotatory product (115 g, $\alpha_D^{21}=+5.60°$ (in substance)) contained 78.5 g of the (+) - enantiomer and has thus an optical purity of 68.2%.

Accordingly, 158.5 g of racemate were resolved into the antipodes in 6½ hours in a reaction space of ½ liter; the space-time yield was accordingly 49 g of antipode/liter/hour.

The crude products could be worked up into the pure antipodes by "drop melting".

EXAMPLE 4

A. 250 g each of racemic 4 - vinyl - azetidinone - (2) (melting point −1°C) were inoculated at −6 to −6.5°C, in the device described hereinbefore and illustrated in Figure 4 of the annexed drawing, with some small crystals of both antipodes. The prepartion of the optically impure, crystalline enantiomers used for the initial inoculation is described hereinafter under B.

The period of each crystallization cycle was 20 minutes, then filtration with suction and exchange of the melts were carried out. After 5 such crystallization cycles, during which the value of the optical rotation of the residual melt oscillated between +1.3° and −1.2° (melt). 280 g of melt were recovered. 114 g of 4 - vinyl - azetidinone - (2) enriched with the (−) - form and having an optical rotation α_D^{21} of −12.1° (melt) and 114 g of the antipode enriched with (+)-form and having an optical rotation α_D^{21} of +10.5° (melt) remained behind in the crystallizers. By repeated melting up and crystallization at 0° to −1°C, there were obtained therefrom, in addition to the racemic melt, pure antipodes having a softening point of +26.8°C and values of the optical rotation α_D^{25} of ±25.94° (substance). The value of optical rotation was found to rise with rising temperature: $\alpha_D^{30}=\pm 27.05°$ (substance).

B. The crystals for the initial inoculation were obtained from 291 g of racemic 4 - vinyl - azetidinone - (2). The lactam was run into 1 liter of 3N - methanolic hydrochloric acid. This solution of the hydrochloric 3 - amino - 4 - pentenoic acid methyl ester was combined with 303 g of triethylamine and the solution of 450 g of L - (+) - tartaric acid in 2 liters of methanol. Upon cooling, 308 g of hydrogen-tartrate of the amino-acid ester crystallized in optically enriched form; melting point 87—90°C, $[\alpha]_D^{21}=+17.3°$ (c=3; water). The hydrogen-tartrate was suspended in 2 liters of methanol, the tartaric acid was precipitated with the aid of ammonia and the amino ester was isolated by distillation under reduced pressure: boiling point: 80°C/25 mm Hg, $n_D^{20}=1.4485$; yield 103 g. $d^{21}=1.001$; $[\alpha]_D^{21}=-17.62°$ (substance); optical purity unknown. Therefrom, there were obtained by cyclization with ethyl-magnesium bromide in ether, 8 g of dextrorotatory 4 - vinyl - azetidinone - (2); boiling point: 110°C/10 mm Hg; $n_D^{20}=1.4855$; $[\alpha]_D^{21}=+10.0°$ (c=3; methanol) with unknown optical purity. From this substance, there was isolated by "drop melting" at +6°C 0.5 g of crystalline material which was used for the initial inoculation.

In the same manner, but using D - (−) - tartaric acid as optical auxiliary, there was obtained the initial (−) - 4 - vinyl - azetidinone.

WHAT WE CLAIM IS:—

1. A process for the separation of the components of a binary mixture (except a binary mixture forming mixed crystals and/or congruently or incongruently melting solid phases) having a minimum melting point in the range of from −100 to +150°C and a composition falling between the extrapolated branches of the melting point curve, which comprises inoculating an homogeneous melt of the binary mixture, with crystals of one of the components at a temperature which is in the range of from 0.05 to 15°C below the eutectic temperature, allowing this component to crystallize selectively until the melt contains substantially less of this component than the eutectic mixture and separating the crystals from the melt.

2. A process as claimed in claim 1, wherein a mixture with a minimum melting point in the range of from −80 to +120°C is used.

3. A process as claimed in claim 1, wherein a mixture with a minimum melting point in the range of from −50 to +110°C is used.

4. A process as claimed in any one of claims 1 to 3, wherein the temperature is 0.5 to 6°C below the eutectic temperature.

5. A process as claimed in any one of claims 1 to 4, which is carried out isothermally.

6. A process as claimed in any one of claims 1 to 5, wherein the binary mixture is the eutectic mixture.

7. A process as claimed in any one of claims 1 to 6, wherein the procedure is repeated with alternating inoculation of both compounds.

8. A process as claimed in any one of claims 1 to 7, wherein the homogenous melt is continuously and isothermally recycled through two crystallizers each containing crystals of one of the components.

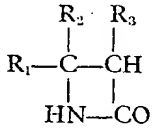
9. A process as claimed in any one of claims 1 to 8, wherein the homogenous melt is continuously and isothermally recycled through two crystallizers each containing crystals of one of the components, while continuously refilling with liquid eutectic phase and continuously separating the formed crystals and removing inoculation crystals when

transferring the melt from one crystallizer to the other.

10. A process as claimed in any one of claims 1 to 9, wherein a binary mixture of organic compounds is separated.

11. A process as claimed in any one of claims 1 to 10, wherein a racemic mixture of optical isomers is separated.

12. A process as claimed in claim 11, wherein a chiral β-lactam of the formula



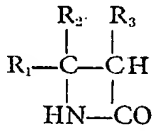
in which R_1 represents a lower alkyl radical having from 1 to 5 carbon atoms, a vinyl radical or a phenyl radical, R_2 and R_3 each represents a hydrogen atom, a methyl radical or together an alkylene radical having from 3 to 5 carbon atoms, with the proviso that if R_1 is the same as R_2, R_3 is not a hydrogen atom, is separated into its antipodes.

13. A process as claimed in claim 1 carried out substantially as described in any one of the Examples herein.

14. A process as claimed in claim 1 carried out as herein described with reference to, and as illustrated in, the accompanying drawings.

15. A component of a binary mixture whenever obtained by a process as claimed in any one of claims 1 to 14.

16. An enantiomer of a β-lactam of the formula



in which R_1 represents a lower alkyl radical having from 1 to 5 carbon atoms, a vinyl radical or a phenyl radical, R_2 and R_3 each represents a hydrogen atom, a methyl group or together an alkylene radical having from 3 to 5 carbon atoms with the proviso that if R_1 is the same as R_2, R_3 is not a hydrogen atom, whenever prepared by a process as claimed in claim 12.

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FIG. 1

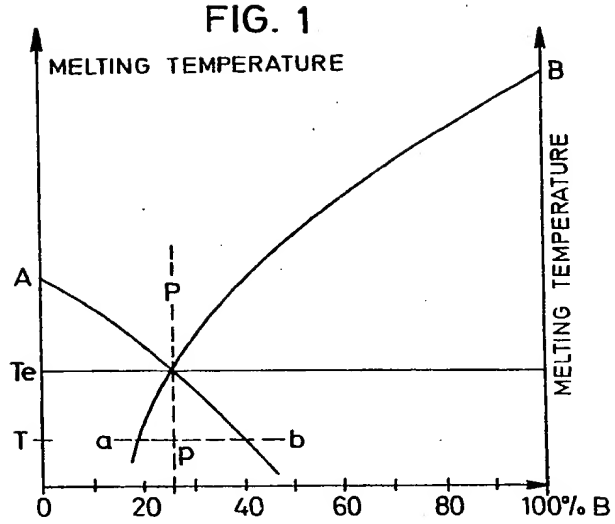

FIG. 2

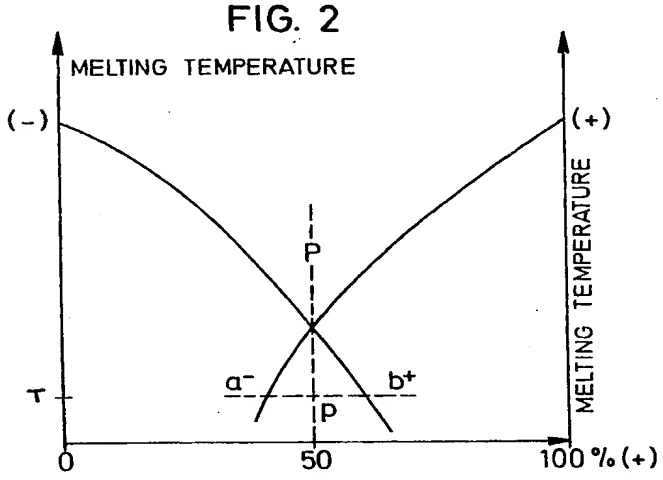

FIG. 3

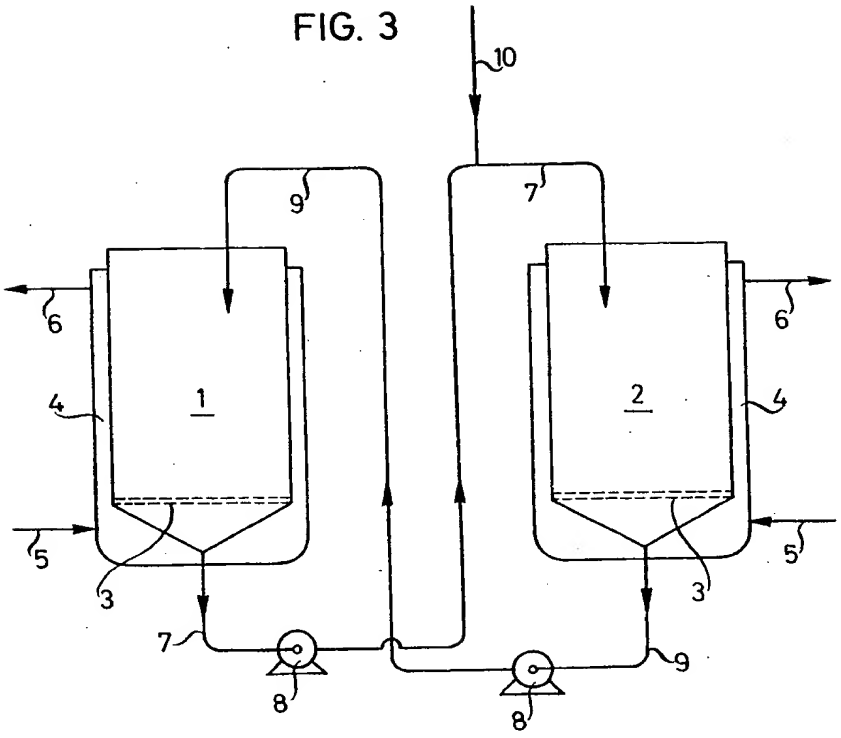

FIG. 4